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ROUNDTABLE DISCUSSION

The Evolution of the CLI Treatment Algorithm

A multidisciplinary panel shares insights on practice patterns, treatment algorithms, and hopes for future solutions for this challenging disease.

WITH RALF LANGHOFF, MD; ROBERT A. LOOKSTEIN, MD; MIGUEL MONTERO-BAKER, MD; AND JIHAD A. MUSTAPHA, MD, FACC, FSCAI

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How would you describe the current critical limb ischemia (CLI) landscape, particularly below-the-knee (BTK) disease?

Dr. Lookstein: The last 5 years have brought about a revolution, and we can now cross 90% to 95% of all lesions. It's not 100%, but it opens opportunities to treat a much broader segment of the population. The unmet need at this point is dense circumferential calcification in the tibial arteries—it is still a technical challenge to cross.

Dr. Montero-Baker: I would agree; we've made immense strides in chronic limb-threatening ischemia therapy. With the development of robust technical skills and more appropriate technology, operators are able to treat more complex and distal disease patterns. This perfect storm of technical skills and advanced tools makes the question of "What's possible?" irrelevant and the question "What's appropriate?" extremely relevant. Overall unmet needs are mainly surrounding intraoperative performance goals. I'm still dumfounded

when I listen to opinion leaders at scientific summits who quote their own personal experience as the basis for a recommendation. I respect and appreciate experience, but we need objective, measurable tools that help us understand the effect of our intervention in the setting of the patient's needs.

Moreover, this is a complex, multidimensional problem. Revascularization, as important as it may be, is really just part of the equation. We can't negate the transcendental impact of risk modification, medical optimization, nutritional support, wound care, podiatric care, and psychological support.

Finally, I also agree that extensive occlusive and calcified disease of the BTK vessels may be the most technically challenging scenario to treat. If you have a target, you can still attempt a few things and be aggressive when scaffolding, but the results—in my view—inevitably end up being less than optimal.

Dr. Mustapha: We are starting to see more patients with stage 3 or 4 chronic kidney disease who are not necessarily on dialysis and may have diabetes. Evolving technical approaches (eg, Schmidt technique, arterial-venous flow reversal, etc) have really transformed the ability to treat the high-percentage occlusions that we used to not even attempt.

What's interesting is the robustness of medical therapy that we have adopted in our practice. With statins, we make sure the patient's LDL (low-density lipoprotein) is < 70 mg/dL and that the HDL (high-density lipoprotein) is somewhat elevated. We send the patients to supervised exercise programs. The patients go on dual antiplatelet therapy and ACE (angiotensin-converting enzyme) inhibitors, if they can tolerate them. There are multiple modalities of medications that are not being utilized in these patients, but we are starting to use them postprocedure. Today in our practice, we put patients on 80 mg of atorvastatin. We use dual antiplatelet therapy, and if the patient's lipid profile is not where it needs to be in 3 months, we add ezetimibe. This has worked really well for our patients, but unfortunately, there are no data in this area for the peripheral arteries, only the coronaries.

Dr. Langhoff: There are numerous innovations that have come along over the last few years, but it is not just the devices that improve outcomes for CLI patients. It is my belief that the access strategy and approach to the target vessel are the main drivers of success. Wire technology is probably the most important issue that interventionalists should be aware of if they want to take on "CLI treatment 2.0." There is so-called sad foot, meaning one that is almost lost because it is so difficult to establish flow due to the missing outflow. It takes a lot of effort here to establish outflow and restore blood perfusion to the wound, and is the most challenging type of case.

THE IMPORTANCE OF CARE COORDINATION AND A TEAM APPROACH IN TREATING CLI

Outside of technical advances, how has the approach to CLI care shifted in recent years?

Dr. Montero-Baker: I think we are coming to an understanding of the importance of a team approach to properly care for these patients. I think solo practitioners who have no collaborative interdisciplinary care will slowly become extinct. We truly need to work cohesively in the patient's best interest. Turf wars, particularly among vascular interventionalists, benefit no one. There is so much we can learn from each other!

The Save the Extremity Program (STEP) nests a group of different individuals who bring a different set of tools that ultimately help patients along their recovery process. For many years, our group has promoted the core model termed, "Toe and Flow." This model emphasizes the elemental role that podiatrists/wound care specialists (toe) and vascular interventionalists (flow) play. Lately, we've recognized the importance of a third core element: functional recovery. This led us to pursue a new model called, "Toe, Flow, and Go." The idea is to emphasize the importance of rehabilitation and independent living as ultimate goals of the care compendium.

Dr. Langhoff: In Berlin, the awareness of our specialty among diabetologists, who see most of our CLI candidates, has developed. They've started to notice a difference when they send their patients to a dedicated center with a CLI team versus an interventionalist or pedal bypass surgeon alone. Working within such a team approach is a great opportunity. As an interventionalist, I depend on the feedback from the wound care team. Sometimes we have patients who require interventions twice within the same hospital stay if the wound does not sufficiently heal. Thorough treatment of the underlying disease and the comorbidities is the influencing factor to change the mortality rate and long-term outcome.

Dr. Mustapha: We have what we call the "virtual multidisciplinary team." The interventionalist sees the patient, performs the necessary procedure, prescribes medication, and then refers the patient to the podiatrist. The podiatrist will see the patient for consultation and decide whether amputation is needed. The same patient will see an infectious disease specialist if they have osteomyelitis. The patient will also see our dietician, who often recommends a specific program that includes hormone injections. The patient completes this cycle within 30 days, and then comes back to us. So far, this virtual team has led to phenomenal outcomes for our patients. The collaboration and communication are key.

How can the team approach be improved upon and expanded to regions that currently do not have a robust multidisciplinary strategy?

Dr. Langhoff: Patients often tend to neglect their disease/disorder. Even when they realize that something is going wrong, it may still take them a while to see a physician. Seizing every opportunity for a CLI team member to evaluate a wound or any other relevant parameters by a software-based system would help dramatically speed up the pathway of individual wound care. Presumably, catching the patient at an earlier stage would lead to a better outcome, and this is more easily achieved if performed with an IT solution. Even in regions with a robust multidisciplinary strategy, a tool that would enable patients to easily show a foot lesion to a care provider would be of great benefit. Some training would be required when integrating these new tools, but nowadays almost everyone can handle a smartphone, for example.

Dr. Montero-Baker: It's never easy to have many cooks in the kitchen. We need to look at how we can improve the longitudinal care experience. I'm excited that Boston Scientific is piloting software to try and improve communication between all team members (specifically with the referring physicians who are the community gate keepers). It's not rare that by the time patients make it to our program, their condition has drastically deteriorated. When asked about the reasons for delay in care, I've been told, "I live 4 hours away," "I couldn't get an appointment," "I couldn't get a referral from the right person at the right time," or "You were out of town."

Dr. Mustapha: We need that improvement in patient communication immediately, especially for CLI patients. We can't FaceTime or receive pictures from our patients on our phones because of the lack of security encryption. Patients who undergo limb salvage procedures come to our office every 2 weeks. If they live far away, I don't want them to have to drive 6 hours every 2 weeks, so it would be phenomenal if I could spend 10 minutes over the phone to see everything.

Dr. Lookstein: CMS is going to change all of this very soon—there is now reimbursement for telephone interviews. The door is cracking open, and I think we're going to have more telehealth opportunities in the future, but it's going to be up to each state to determine what is safe. I think we all agree that remote surveillance is an unmet need in terms of the ability to send a patient out of the building and be able to remotely assess the perfusion at a week, 30 days, and 60 days.

Dr. Montero-Baker: Prospective knowledge can become crucial in decision making for reintervention and preventing unnecessary readmissions. The development of telemedicine and patient-directed, user-friendly interfaces is going to be interesting (eg, photography, sensors, thermometers, etc). An example of such disruptive technology are "smart socks" (from companies such as Siren) that embeds smart threads into a sock to measure subtle changes in temperature. The principle relies on the known fact that before clinically significant breakdown, there is an increase in skin temperature in the diabetic foot. In my opinion, having systems in place to silently capture the data, process it via artificial intelligence protocols, and deliver it to the caregiver will revolutionize medicine.

Dr. Mustapha: Recently in our practice, we have had this discussion about how great it would be for the patient to have something they put on the foot that we can use to measure perfusion. The future right now is in those two elements—telemedicine and a means of measuring perfusion. To be able to tell my CLI patients, "You can stay home, you don't have to drive 2 hours to get to your appointment today," I would love to see that come to life sooner rather than later.

DCB VERSUS DES IN A TREATMENT ALGORITHM

What do you think the role of BTK drug-coated balloons (DCBs) and drug-eluting stents (DESs) will be? Are both technologies needed?

Dr. Mustapha: In the first positive DCB trial, long lesions actually responded better than the shorter lesions, which is really reassuring for us.[1] It allows us to tackle the anatomy that scares us interventionalists most, which is the distal portion of the tibial artery just as it becomes the peroneal artery. The distal tibial arteries will benefit the most from proper DCB therapy, as will the ostia of other arteries (eg, going from the tibial peroneal trunk into the peroneal across the anterior tibial and posterior tibial arteries).

On the other hand, scaffolding is phenomenal, and I think scaffolds will be especially beneficial in the proximal anterior tibial and proximal posterior tibial arteries, because this is where dissections most frequently occur. Additionally, if you use a DCB for an intervention and get great results in 90% of the vessel, but there is a flow-limiting dissection in 10% or 20% of it, then you need some way out—now we will finally have scaffolding for that anatomy. This is why I think both BTK DCBs and DESs are extremely valuable.

Dr. Langhoff: Yes, I guess both technologies are needed, although the Lutonix BTK trial is the only trial to date showing positive results with BTK DCB technology.[1] All three of the BTK DES trials had been positive.

The major difference is the lesion location. We stay away from placing BTK stents distally. Proximal, focal lesions do quite well with DESs, but the longer ones will probably benefit more from a DCB, as shown in the Lutonix BTK interim analysis. I am looking forward to the first nitinol-based DES from Boston Scientific, which is currently under investigation;

it could turn out to be a game changer. It makes sense to offer longer BTK DESs than those of the coronary platform.

Dr. Lookstein: What do you think the relative need is for scaffolds versus DCBs?

Dr. Montero-Baker: When it comes to chronic total occlusions (CTOs), yes, we have crossing devices and reentry techniques, but that subgroup of lesions may have the most acute recoil. I explain to patients that we are essentially moving a huge column of cement to the side. We may get that little trickle of flow along its side, but in a day, a week, or a month, it will probably just move back to where it was. It is in those patients that I am very adamant about scaffolding.

Unfortunately, some of these are very long lesions, and scaffolding an entire tibial vessel may be overly aggressive. I do believe in some circumstances, it may be the right thing to do to prevent poor long-term or even midterm results. I'm excited to see what technology like the Tack endovascular system (Intact Vascular, Inc.) or the Saval™ DES BTK (Boston Scientific Corporation) will offer, as they may open the doors to efficiently treating more complex BTK disease patterns.

Dr. Lookstein: I agree with that. Calcium in the BTK circulation isn't going away any time soon. Crossing calcium is certainly technically feasible, but it is challenging, and we're treating more challenging patients. I am skeptical that a DCB is going to be able to tackle that, especially as we're dealing with 15- to 30-cm–long lesions. I think DCBs will have their place, but probably not for calcified lesions.

I'm apprehensive about leaving behind a suboptimal result after using a DCB in a patient with an open wound. I am a big believer in scaffolds, and I have heard those stories of peripheral interventionalists using more coronary stents than some of the cardiologists, illustrating the need for stents of that size. I clearly think that the Saval™ DES BTK and any other BTK scaffolds are going to deal with a very significant unmet need.

Dr. Mustapha: The Saval™ DES BTK is going to be a paradigm-shifting tool when it comes out. In the cadaver work that we did, the one unexpected thing we discovered in the tibial arteries was a double layer of smooth muscle cells with different functions. Because of that, we need a tool like the Saval™ DES BTK that has prolonged drug elution. Many don't understand why we need to elute for that length of time. The proliferation or migration of smooth muscle cells in the tibial arteries act completely differently than any other arterial bed in the body. In the coronary arteries, we found five layers, and in the tibial arteries, there are 20 layers, and they actually function. Because of that, the prolonged drug elution of the Saval™ DES BTK will make it our primary scaffold type.

Dr. Lookstein: I agree, 100%. Is there also going to be a reemergence of bioabsorbable scaffolds for this anatomic region? Right now, it doesn't appear so, but I think everybody would agree that maybe we should look at that again in the future. We have to figure out what the exact roles of DCBs and DESs are, and only at that point will we be able to reengage with bioabsorbable scaffolds.

Dr. Mustapha: If you look at recoil in the tibial artery, the highest rates of recoil are actually in the midportion of the vessel, not at the takeoff level of the anterior to posterior tibial artery. We are conducting studies on recoil and have been using intravascular ultrasound (IVUS) in long CTOs. Due to what we've observed on IVUS, we have realized that the smallest available JETSTREAM™ Atherectomy System (Boston Scientific Corporation) achieves better vessel preparation than anything else that I know of. We used to think it was too bulky for the tibial arteries, but based on IVUS, which is the key, the luminal gain we're getting at the end of this procedure is phenomenal.

PERSPECTIVES ON THE RECENT PACLITAXEL DATA AND CURRENT DRUG-ELUTION TREATMENT ALGORITHM

What is your perspective on the recent data related to paclitaxel-coated devices?

Dr. Lookstein: I believe all vascular specialists are concerned about the conclusions of the meta-analysis. I am looking forward to reviewing patient-level data and participating in prospective research to put this issue to rest. Hopefully this will allow a return to a culture where antiproliferative therapy is once again considered standard of care for symptomatic occlusive disease in the femoropopliteal arteries.

Dr. Mustapha: I personally have not changed my practice. I continue to use paclitaxel-coated balloons just as before. We did add the recommended step of informed patient consent. But our overall approach is still the same.

Dr. Langhoff: There is no panic or fear from my side. I think we have to look at this carefully, and I strongly support all of the principal investigators of recent paclitaxel-based trials who are aiming for a 5-year mortality endpoint to collect data on this issue. When I follow the lectures that explain and analyze the Katsanos group's findings, I more and more doubt the reliability of this dataset, because the group samples were miscalculated in terms of crossover procedures and those lost to follow-up, which makes a major difference.

The benefit of this technology is so overwhelming that we have not changed our treatment algorithm so far.

Dr. Montero-Baker: Katsanos et al have shed light on a very sensitive matter. The signal should not be brushed off. That said, I don't agree with the total opposite, meaning overreacting to a particular data set analysis. Responsible and critical analysis is crucial for safer patient interventions. Moreover, not all data related to currently approved market devices were included in this analysis. Also, the most significant conclusions are a matter of associational nature, ignoring true causation. Finally, patient-level data are scarce and overall missing. Health agencies are currently analyzing the data in-depth, and I would defer to them for guidance. For now, I will continue my practice using medication-enhanced devices on case-by-case bases.

BELOW-THE-ANKLE TRENDS AND THE NEED FOR PURPOSE-BUILT TECHNOLOGIES

As the paradigm shifts to allow operators to intervene below the ankle, are the currently available devices adequate? What technologies are still needed, and is there a role for antiproliferative therapy in this area?

Dr. Mustapha: The Savion™ Guidewires (Boston Scientific Corporation) maneuver phenomenally below the ankle; they have done great things for us, especially if you have a pedal loop. I'm a big supporter of opening the artery to the segment where the ulcer is located and delivering blood there directly. Below-the-ankle therapy is a must if there is an occlusion, because if you don't have a good outflow, wound care and medical therapy are not going to help, no matter what you do. Today, we are limited to balloon angioplasty; there is not much more to do.

Dr. Lookstein: We need dedicated devices. I believe there is a growing recognition that the status of the plantar vessels is critical to wound care and limb preservation for patients with advanced disease. I think experienced operators are compulsively performing more pedal angiography and assessing the patency of the plantar circulation, and if the skill set is there, they are doing anything they can to improve or open the circulation through the plantar vessels.

That is a skill set that is not globally uniform, but I think it is being recognized as the next frontier and a growing clinical need. Unfortunately, I frequently have patients sent to me for a second or third opinion, and the supplied films don't show anything below the ankle because the imaging was never performed. We need to educate the clinical teams who are caring for these patients that pedal angiography is critical, and if the status of the plantar vessels is compromised, then the patient should be sent to a specialist who knows how to access those vessels with a guidewire or bypass.

Dr. Mustapha: What is your go-to microcatheter that you use to maneuver across the tibial circulation when you do a pedal loop?

Dr. Lookstein: I will typically use a 0.018-inch support catheter because it has a little more body to it, or I'll use a 0.014-inch over-the-wire balloon—Coyote™ (Boston Scientific Corporation) is great, as well as several other over-the-wire balloons. I strongly prefer doing these cases from an antegrade approach. I think using a contralateral approach is just asking for trouble on multiple levels. It all depends on your setup and whether you believe it is more facile and more efficient with your time to use an over-the-wire balloon or to use a support catheter.

Dr. Montero-Baker: I primarily use Coyote™ as support because I believe it saves a step. When I do use a support catheter, I like the 0.014- and 0.018-inch braided CXI® Support Catheters (Cook Medical). For most retrograde accesses, I do not use a sheath. There are compelling data from our colleagues in Japan that show that when you achieve substantial wound blush, the curves for healing significantly diverge.[2] I'm happy to see that we are now seriously starting to develop some objective performance goals.

The reality is that we need tools to further assess our results and, moreso, make some timely on-table decisions. I think the development of technology like two-dimensional perfusion angiography or implantable microsensors will drive the adoption and acceptance of below-the-ankle interventions. If we can show that these procedures provide good perfusion, then we can tell ourselves—and more importantly, our colleagues who are referring the cases—that we have achieved an established goal (which further leads to adequate wound healing). It would be amazing to think that in the near future, we could come up with some clear-cut perfusion levels that could easily be interpreted by our foot surgeons/podiatrists in order to establish therapy benchmarks.

Dr. Langhoff: Vessels below the ankle are very small, and we mostly treat the "sad foot" patients. Personally, I have no experience with drug-coated devices in these arteries, as they are often very calcified and hence are not the proper scenario for DCB use.

I learned a lot from my Japanese colleagues and friends, and in my lab, we spend our efforts using wire technology and support catheters, which I think have taken a major step forward in being able to open even very distal and challenging lesions through a bidirectional approach. Around 90% of these procedures are finalized with PTA only.

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THE FUTURE OF CLI: WISHLIST DEVICES, COMPARATIVE-EFFECTIVENESS DATA, AND PATIENT-CENTERED OUTCOMES

We've discussed the need for developments in telemedicine, but what other unmet needs remain in the CLI space?

Dr. Mustapha: In terms of devices, we need a microcatheter for the pedal circulation. Many patients come to us with a dissected pedal artery or transmetatarsal artery, because a previous intervention shoved a catheter up and ruined the pedal circulation.

Dr. Lookstein: What about a reliable reentry catheter for the balloon recirculation?

Dr. Mustapha: That would be an amazing thing to have. As we continue to collect IVUS data on long tibial CTO crossing, we have learned many important technical steps to help fill some of the current unmet needs. IVUS-directed CTO crossing via the subintimal space using wires in the tibials is extremely helpful and provides factual feedback to the operator and assists in choosing the best possible treatment modalities. If IVUS shows the crossing wire to be just under the endothelial luminal layer, this allows for almost all therapeutic options, including catheter-based crossing techniques. On the other hand, if the IVUS feedback shows the crossing wire to be deep into the vessel wall (ie, deep media or adventitia), the therapeutic options become very limited and the risk of complications becomes high. Hence, we have the terminology of *deep wall crossing,* which is unfavorable and associated with untoward outcomes. We also have subendothelial or subintimal crossing, which has much more favorable outcomes and allows for the dual antegrade/retrograde catheters crossing technique, leading to easy reentry into the true lumen.

Dr. Lookstein: I think guidewires could clearly be improved upon. I'm excited that the FDA now recognizes that there are unmet clinical needs for this patient population and that trials are going through an expedited pathway. I'm hoping we will soon see a number of devices that are on label for the treatment of CLI in North America. I think an unmet need is comparative-effectiveness research for this anatomic space to prove which therapy works best.

Dr. Langhoff: Wires, wires, and once again wires—they make the difference! Beyond all endovascular approaches, the recruitment of collaterals is an unmet need. A drug or maybe noninvasive counterpulsation that may create better oxygen perfusion to the tissue could be the answer to failed endovascular procedures or bypass surgery. This is still a matter of basic science.

Venous arterialization is also very interesting as a bailout strategy. However, I believe there should be something performed before giving up the arterial pathway to restore oxygen perfusion via the venous side of the collateral bed.

Dr. Montero-Baker: Not all of the efforts in trying to facilitate appropriate patient care may lead to a lot of money making; I think there needs to be investment in the science itself—creating objective performance goals, optimizing our intraoperative data, and better assessment of intraoperative efficiency. I would like to find more support on other research parameters as goals for CLI. I think we should move away from target lesion revascularization (TLR) and find some wound-based, quality-of-life, and/or true walking assessment. We have to change the way studies are performed. We don't have to ignore patency, because it is important to avoid bringing the patient back over and over, but ultimately, the problem is that ischemic wounds don't do well. We need to cure the wounds and make the patient's pain go away and get them back into society.

As we develop more research projects, we should be open to changing the endpoints that we have been adhering to for the last 15 years. We're mature enough as a field now to understand that CLI requires different endpoints moving forward.

Dr. Lookstein: There is a tremendous amount of opportunity to identify patient-centered outcomes related to CLI. To Dr. Montero-Baker's point, freedom from TLR is not the most important variable for a majority of our patients. Pain is a huge driver for this demographic. I don't think we're doing enough to really identify whether an endovascular or surgical approach successfully alleviates pain with or without tissue loss at 6 months or 1 year and how that contributes to someone being able to work, ambulate, and take care of themselves. Much of what contributes to patients' everyday quality of life is independence and how that affects their mood and their ability to be opiate free.

If the entire community treating these patients can embrace a more patient-centered approach, we will hopefully soon identify the best treatment strategy to improve patients' quality of life, not just achieve freedom from TLR. We've been centered on whether the artery is open, and that's only a small piece of the puzzle. We are talking about people who have lost their ability to control their own lives, and we all want to give them control of their lives back and make them functioning members of this global entity. There is a lot of room for improvement there. ■

1. Mustapha JA. Lutonix below-the-knee global DCB IDE study: primary endpoint outcomes at 6 months. Presented at: VIVA 18; November 7, 2018; Las Vegas, NV.
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